

CLAIMS

1. A method for producing a sustained-release composition, which comprises mixing an aqueous solution containing a physiologically active substance and an acid or base in a molar amount of about 1.5 or more times that of the physiologically active substance with a solution of a biodegradable polymer, and then drying the mixture.
2. The method according to claim 1, wherein the aqueous solution is obtained using a salt of the physiologically active substance with the acid or base.
3. The method according to claim 1, wherein the proportion of the physiologically active substance in the sustained-release composition is about 0.001 to about 50% by weight.
4. A method for stabilizing a mixture of an aqueous solution containing a physiologically active substance and a solution of a biodegradable polymer, which comprises adding an acid or base in a molar amount of about 1.5 mol or more times that of the physiologically active substance.
5. A method for allowing a mixture of an aqueous solution containing a physiologically active substance and a solution of a biodegradable polymer to have a viscosity of about 3,000 cp or less, which comprises adding an acid or base in a molar amount of about 1.5 mol or more times that

of the physiologically active substance.

6. The method according to any one of claims 1, 4 and 5, wherein the physiologically active substance is a physiologically active peptide.

5 7. The method according to claim 6, wherein the physiologically active peptide is an LH-RH derivative.

8. The method according to claim 7, wherein the LH-RH derivative is a compound represented by the general formula:

10 5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z

wherein Y represents DLeu, DAla, DTrp, DSer(tBu), D2Nal or DHis(ImBzl) and Z represents NH-C₂H₅ or Gly-NH₂.

9. The method according to any one of claims 1, 4 and 5, wherein the acid or base in a molar amount of about 1.5 to
15 about 5 times that of the physiologically active substance is used.

10. The method according to any one of claims 1, 4 and 5, wherein the acid or base in a molar amount of about 1.65 to about 3 times that of the physiologically active substance
20 is used.

11. The method according to any one of claims 1, 4 and 5, wherein the acid is an organic acid.

12. The method according to claim 11, wherein the organic acid is a fatty acid.

25 13. The method according to claim 12, wherein the fatty

acid is acetic acid.

14. The method according to any one of claims 1, 4 and 5, wherein the biodegradable polymer is an α -hydroxycarboxylic acid polymer.

5 15. The method according to claim 14, wherein the α -hydroxycarboxylic acid polymer is a lactic acid-glycolic acid polymer.

16. The method according to claim 15, wherein the molar ratio of lactic acid to glycolic acid in the lactic acid-glycolic acid polymer is 100:0 to 50:50.

17. The method according to claim 16, wherein the molar ratio of lactic acid to glycolic acid in the lactic acid-glycolic acid polymer is 100:0.

18. The method according to claim 15, wherein the weight average molecular weight of the lactic acid-glycolic acid polymer is 5,000 to 50,000.

19. The method according to claim 15, wherein the weight average molecular weight of the lactic acid-glycolic acid polymer is 17,000 to 30,000.

20. The method according to claim 1, wherein the biodegradable polymer is a lactic acid polymer having a weight average molecular weight of 15,000 to 50,000 and the content of a polymer having a weight average molecular weight of 5,000 or less in said lactic acid polymer is 5% by weight or less.

21. The method according to claim 1, wherein the biodegradable polymer is a lactic acid-glycolic acid polymer having about 20 to about 1,000 μmol of terminal carboxyl per unit mass (gram) of the polymer.

5 22. The method according to claim 1, wherein the molar amount of the terminal carboxyl of the biodegradable polymer is about 0.1 to about 5 times that of the physiologically active substance.

23. The method according to any one of claims 1, 4 and 5,
10 wherein the solution of a biodegradable polymer is prepared using a low water-soluble organic solvent.

24. The method according to claim 23, wherein the low water-soluble organic solvent is dichloromethane.

25. The method according to any one of claims 1, 4 and 5,
15 wherein the mixture is a homogeneous mixture.

26. The method according to claim 25, wherein the homogenous mixture is an emulsion.

27. The method according to claim 26, wherein the emulsion is a W/O type emulsion.

20 28. The method according to claim 27, wherein the particle size of the W/O type emulsion is very small.

29. The method according to claim 1, wherein the drying of the mixture is in-water drying.

30. The method according to claim 29, wherein an aqueous
25 solution of an osmotic pressure regulating agent is used as

an outer aqueous phase on the in-water drying.

31. The method according to claim 30, wherein the osmotic pressure regulating agent is mannitol.

32. The method according to claim 1, wherein the
5 sustained-release composition is in the form of a microparticle.

33. The method according to claim 32, wherein the microparticle is a microsphere or a microcapsule.

34. A method for producing a sustained-release composition,
10 which comprises mixing an aqueous solution containing 1) a physiologically active substance and 2) an acid or base in an amount of about 0.1 to about 20% by weight of said aqueous solution with a solution of a biodegradable polymer, and then drying the mixture.

15 35. The method according to claim 34, wherein the aqueous solution is obtained using a salt of the physiologically active substance with the acid or base.

36. A sustained-release composition produced by the method according to claim 1.

20 37. A use of an aqueous solution containing a physiologically active substance and an acid or base in a molar amount of about 1.5 or more times that of the physiologically active substance, for producing a sustained-release preparation containing the
25 physiologically active substance.